Health Canada Santé Canada

September 19, 2011

Notice

Our file number: 11-116834-899

Subject: Release of the Final Guidance Document *Data Requirements for Safety and Effectiveness of Subsequent Market Entry Steroid Nasal Products for Use in the Treatment of Allergic Rhinitis* for Industry

Application

This guidance is intended to assist sponsors in the collection and analysis of data for Steroid Nasal products for use in the treatment of allergic rhinitis, in order to meet the safety and effectiveness requirements under Part C, Division 8 of the *Food and Drug Regulations*. The data and standards outlined in this guidance are intended to be applied to a new steroid nasal product being compared to a product for which clinical safety and effectiveness data exist. For clarity, these types of products will be called "Subsequent Market Entry Products".

Context

Health Canada is pleased to announce the release of the final version of the Guidance Document *Data Requirements for Safety and Effectiveness of Subsequent Market Entry Steroid Nasal Products for Use in the Treatment of Allergic Rhinitis.* Comments and suggestions received from the consultation on the draft version of the Guidance were reviewed and considered in the finalization of this Document.

The initial Draft Guidance Document dated August 1, 2007 was posted on Health Canada's website for Stakeholder consultation. The comments received during this consultation process, together with discussions and changes to the Guidance Document, have been collated in a separate *Questions and Answers Document*, which is available *upon request.* Requests for this *Questions and Answers Document* should be directed to the mailing and/or email address given below.

Should you have any questions or comments regarding the content of the Guidance, please contact

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Health Canada Santé Canada

GUIDANCE DOCUMENT

Data Requirements for Safety and Effectiveness of Subsequent Market Entry Steroid Nasal Products for Use in the Treatment of Allergic Rhinitis

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Minister of Health

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Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

Également disponible en français sous le titre : Ligne directrice - Exigences relatives à l'innocuité et l'efficacité des stéroïdes pour pulvérisation nasale de commercialisation subséquente utilisés dans le traitement de la rhinite allergique

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent, and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy, or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1. INTRODUCTION

1.1 Policy Objectives

This guidance is intended to assist sponsors in the collection and analysis of data for Steroid Nasal products for use in the treatment of allergic rhinitis, in order to meet the safety and effectiveness requirements under Part C, Division 8 of the *Food and Drug Regulations*. The data and standards outlined in this guidance are intended to be applied to a new steroid nasal product being compared to a product for which clinical safety and effectiveness data exist. For clarity, these types of products will be called "Subsequent Market Entry Products".

1.2 Policy Statements

Total Nasal Symptom Scores (TNSS) should be collected in an appropriately designed study.

The TNSS should be analyzed accordingly such that the 90% confidence interval of the relative means for the test over reference is completely contained within the equivalence interval of 80-125%.

Systemic blood levels of the active substance should be measured and meet the usual bioequivalence standards for uncomplicated drugs.

1.3 Scope and Application

This guidance is intended to be applied to all submissions involving the demonstration of therapeutic equivalence in order to provide pivotal evidence of the safety and efficacy of a new Steroid Nasal Product for use in the treatment of Allergic Rhinitis. Examples of cases where this guidance applies are:

a) therapeutic equivalence studies in support of the equivalence of Subsequent-Entry Products to the Canadian Reference Product [Abbreviated New Drug Submission (ANDS)];
b) bridging studies where the formulation to be marketed is different from the formulation used in the pivotal clinical trials [New Drug Submission (NDS), Supplemental New Drug Submission (SNDS)];
c) studies in support of significant post-marketing changes and line extensions [Supplemental Abbreviated New Drug Submission (SANDS), SNDS)].

This guidance applies to steroid nasal products including only one active ingredient. It does not apply to combination products.

1.4 Background

Rhinitis is a common condition and although it is not life-threatening it can severely affect the quality of a patient's life with nasal obstruction, sneezing and rhinorrhoea resulting in repeated nose blowing, poor sleep, limited social interaction, impaired concentration and headache (Macky, 1997).

Topical nasal corticosteroids have become a mainstay treatment for the symptoms of allergic rhinitis. The benefits of topical drug administration for rhinitis include a low risk of systemic adverse effects, a quick onset of action, and good therapeutic effect (Mygind, 1997).

This guidance document has been prepared by the Bureau of Cardiology, Allergy and Neurological Sciences (BCANS) in collaboration with the Office of Sciences (OoS), Therapeutic Products Directorate (TPD), Health Canada. Advice generated through consultation sessions and teleconferences with the Science Advisory Committee on Respiratory and Allergy Therapies (SAC-RAT) led to the development of this guidance document. Drug sponsors have been given the opportunity to submit podium and/or written presentations before the SAC-RAT.

2. GUIDANCE FOR IMPLEMENTATION

2.1 Requirements

2.1.1 General Filing Requirements for Subsequent Market Entry Steroid Nasal Products

This Guidance should be read in conjunction with the following:

"Guidance for Industry: Pharmaceutical Quality of Inhalation and Nasal Products" (Health Canada, 2006). This guidance provides information on the data requirements related to pharmaceutical quality.

"Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in CTD Format" (Health Canada, 2004). This guidance provides information on how to file in the CTD format.

2.1.2 Requirements for Steroid Nasal Products in Solutions

Drug sponsors may be exempt from the requirement to conduct comparative bioavailability, pharmacodynamic and/ or clinical studies for Subsequent Market Entry drug Products formulated as solutions, since *in-vitro* studies may provide sufficient information to support a proposal of equivalence to the Canadian Reference Product. In order for a product to be considered for exemption, a scientific justification for waiver of such studies must be submitted and found to be acceptable. This justification should include:

- Evidence that the Subsequent Market Entry Product contains the identical medicinal and non-medicinal ingredient(s) in the same concentration(s) as the Canadian Reference Product, and that both products are solutions; and
- Comparison of relevant pharmaceutical characteristics and performance of the delivery system of the two products as outlined in the Health Canada *"Guidance for Industry: Pharmaceutical Quality of Inhalation and Nasal Products"* (Health Canada, 2006).

2.1.3 Requirements for Steroid Nasal Products of Complex Formulations

Products of complex formulations include, but are not limited to emulsions and suspensions. Due to the complexity of these formulations, extensive comparative testing of the pharmaceutical characteristics and performance of the delivery system will not suffice to demonstrate equivalence with the Canadian Reference Product. Therefore, direct evidence of comparative safety and efficacy, through well-designed comparative clinical trials with appropriate outcome measures, must be provided to demonstrate equivalence with the Canadian Reference Product. For most products, this would require using the same clinical endpoint(s) with which the Canadian Reference Product was granted a Notice of Compliance. However, in certain instances alternate clinical endpoints may be acceptable where advances in clinical medicine support that these are commonly used and accepted for the therapeutic indication(s) of interest at the time of application.

The systemic exposure of the steroid must be examined in a comparative bioequivalence study. Should blood or plasma levels be too low to allow for reliable analytical measurement, the equivalence for systemic exposure may be carried out by measuring the steroid side effects on the hypothalamic pituitary-adrenal axis (HPA).

2.1.4 Therapeutic Equivalence Study Requirements for Subsequent Market Entry Steroid Nasal Products

The following study is required when using patients with seasonal allergic rhinitis[a]:

An adequately designed, well controlled, double blinded, randomized study in which patients with seasonal allergic rhinitis (SAR) are randomized into three parallel arms: Canadian Reference Product (R), Subsequent Market Entry Product (T), and Placebo (Formulation Placebo) (P).

Study blinding is a critical consideration, and it is recommended that a description of how the T, R, and P products are to be masked be carefully described in the study protocol.

[a] As alternate, a well-designed, adequately controlled study may be conducted in a standardized Environmental Exposure Chamber. This technique makes the study amenable for cross-over design. Adequate validation data and justification of using this alternate must be filed in the submission.

It is recommended that the study be multicentre to avoid potential investigator bias.

If the run-in period includes placebo, then placebo responders could be excluded prior to randomisation. However, this practice is not recommended because it may obscure the results of the study.

Study Population

Patients with a minimum two-year history of seasonal allergic rhinitis with confirmed positive test for relevant specific allergens (for example [e.g.] allergen skin test) are eligible to be included in the study. Patients with other significant diseases including asthma, with the exception of mild intermittent asthma, should be excluded.

Calculations should be done to ensure there is a reasonably powered sample size in order to demonstrate therapeutic equivalence.

Pollen Count Documentation

Pollen counts should be documented during the study and filed with the study results.

Study Duration

Study duration encompasses a two to three-week treatment period, depending on the onset of action of the study drug, plus at least a three-day run-in period. Placebo dosing is not required for the run-in period.

Scoring and Baseline

Whether the drug is labelled for once or twice daily dosing, clinical evaluations should be made at least twice daily (AM and PM, 12 hours apart, at the same time daily) throughout the study in order to assess potential loss in magnitude of efficacy at 12 hours vs. 24 hours.

Symptom scores should be collected at baseline and daily over the course of the trial. Patients should record scores in a diary at least as often as the daily dosing interval. An appropriate primary efficacy endpoint is the change from baseline in the Total Nasal Symptom Score (TNSS) for the entire double blind treatment period (2-3 weeks).

The clinical evaluations should be made just prior to the treatment administration, especially if the drug is used twice daily, for reflective TNSS. For instantaneous TNSS, the measurement should be made at the AM evaluation.

The preferred measures of effectiveness in allergic rhinitis trials are patient self-rated instantaneous and reflective composite symptom scores. These summed scores generally include the following four nasal symptoms: rhinorrhoea, nasal obstruction, nasal itching, and sneezing, rated on a 0-3 scale of severity. While patient self-rated symptom scores and physician-rated scores can be used, the patient-rated scores are preferred as the primary measure of effectiveness.

A common allergic rhinitis rating system that has been used in clinical trials is the following 0-3 scale:

- 0 = absent symptoms (no sign/symptom evident);
- 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated);
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable);
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

A detailed description of the symptom rating scale should be provided to patients. This should include instructions on proper completion of the symptom diary and definitions of the different categories in the scale.

Baseline is defined as "the mean of three days of off-treatment run-in, plus day-one morning pre-treatment level". Subjects who maintain an average score of at least six over the three days will be eligible for randomization.

Choice of Dose(s)

The choice of dose(s) used in the study should be justified by the subsequent market entry sponsor. However, it should be within the range of dose(s) recommended in the labelling of the Canadian Reference Product and should be maintained throughout study. Generally, the lowest dose marketed by the sponsor of the Canadian Reference Product is recommended for the equivalence study.

Study Outcome Variables

The primary outcome measure should be the average AM+PM Reflective Total Nasal Symptom Scores (TNSS). The Immediate (instantaneous) TNSS should also be evaluated as a secondary measure.

The primary efficacy endpoint is the change from baseline in the TNSS between two treatment groups for the entire double-blind treatment period (2-3 weeks).

Safety assessments, including nasal examination, should be made in advance of treatment (at screening or baseline) and upon conclusion. Adverse events should be reported daily.

Onset of Action

The test product should demonstrate a statistically significant mean difference in TNSS compared to placebo over the initial 5-7 days. The test and reference products should not be significantly different.

Historical Efficacy

The test product and the reference product should demonstrate a statistically significant difference from placebo with regard to the primary efficacy endpoint (AM+PM reflective TNSS). The sponsor should provide information that when compared with placebo, the absolute difference in the TNSS mean change from baseline of the reference product in the current trial is comparable to its historical performance.

Therapeutic Equivalence Criteria

The average of all scores' (e.g. days 1-21) change from baseline for the Subsequent Market Entry (SME) Product (T) and Canadian Reference Product (R) must be significantly different from the placebo. Test and reference should not be significantly different from one another.

To demonstrate the bioequivalence of the test (T) product compared with the reference (R) product, the 90% confidence interval (CI) of the T/R ratio of mean change from baseline of the TNSS score must be within 80% to 125% based on log-transformed data or untransformed data. The choice between using log-transformed or untransformed analysis is to be made based on model check of the TNSS score (Baseline score minus Final score). The facilities for assessing normality within the SAS statistical package plus a thorough visual inspection of various plots of the data are usually sufficient. The scale that renders the data closer to normality is the scale to be used. To use the log scale, first add a constant 6 to the TNSS score change and then apply the log-transformation. [that is (i.e.) log t' = log (t + 6) and log r' = log (r + 6)]. The constant 6 is added to avoid any occurrence of a negative score change.) After transformation, check normality again. If the log-transformed data is closer to normality, then the log-transformed data can be used to demonstrate bioequivalence. Otherwise, use the original scale. When using log-transformed data, perform the inverse transformation to obtain T' and R', and then remove the constant 6 before forming the T/R ratio and the 90% CI.

If equivalence is shown in either SAR or Perennial allergic rhinitis (PAR) patients, the products would be assumed to be equivalent in both.

2.1.5 Clinical Study Requirements for Systemic Exposure to Subsequent Market Entry Steroid Nasal Products

Systemic exposure must be shown to be comparable between the test (T) and the reference (R) products. Data may be obtained from a pharmacokinetic (PK) study evaluating the systemic exposure following nasal administration of the Subsequent Market Entry Nasal Steroid Product relative to the Canadian Reference Product as a surrogate for possible long-term systemic effects.

The PK study should be a single dose study at the upper limit of the dosing range (the maximum labelled adult dose) in which the following PK parameters should be determined: Area under the curve to the last quantifiable concentration (AUC_T), Area under the curve to infinity (AUC_I), Maximum observed concentration (C_{max}), Observed time at which C_{max} occurred (t_{max}), Half-life ($t_{1/2}$) and Terminal elimination rate constant (K_{el}). The study should be conducted with reference to the Health Canada guidance document entitled *"Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies. Part A: Oral Dosage Formulations used for Systemic Effects"* (Health Canada, 1992) which indicates that adult healthy volunteers are preferred.

The following standards will be applied to the PK study, based on log-transformed data:

- The 90% confidence interval of the relative mean AUC_t of the test to reference product should be between 80 and 125%;
- The relative mean measured C_{max} of the test to reference product should be between 80% and 125%.

Should blood or plasma levels be too low to allow for reliable analytical measurement, systemic exposure should be determined in a pharmacodynamic (PD) study by assessment of the effect on HPA axis.

A PK study for systemic exposure would be preferred to a PD study for systemic absorption. If a sponsor has convincing data based on unsuccessful attempts to conduct the PK study, a PD study for systemic absorption could be used.

The PD study should be single or multiple dose study in which the test and reference steroid nasal products are compared. The sponsor is to give supporting rationale for choice of dose(s). The serum cortisol is measured, after dosing, every two hours for 24 hours and the effect is expressed as the serum cortisol area under the 24-hour curve (SCO-24 AUC). The study should be conducted with reference to the *"Report of a Committee of the Canadian Thoracic Society on Comparative Assessment of Safety and Efficacy of Inhaled Corticosteroids"* (Boulet, 1998) and the Health Canada guidance document entitled: *"Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies. Part A: Oral Dosage Formulations used for Systemic Effects"* (Health Canada, 1992).

The following standard should be applied to the PD study based on either log or original scale (see method for model check described in section 2.1.4):

- The 90% confidence interval of the relative mean SCO-24 AUC of the test to reference product should lie between 80% and 125%.

3. ENQUIRIES

For questions, clarification, and further assistance concerning the preparation and filing of submissions for Subsequent Market Entry Steroid Nasal Products, contact the Bureau of Cardiology, Allergy and Neurological Sciences (BCANS) at the following e-mail address: BCANS_enquiries@hc-sc.gc.ca

For questions, clarification, and further assistance pertaining to the design and conduct of clinical pharmacokinetic studies assessing the systemic exposure of the Subsequent Market Entry Products, contact the Bureau of Pharmaceutical Sciences (BPS), Division of Biopharmaceutics Evaluation at the following e-mail address: BPS_ enquiries@hc-sc.gc.ca.

4. GLOSSARY OF ABBREVIATIONS

ANDS Abbreviated New Drug Submission
AUC_I Area under the curve to infinity
AUC_T Area under the curve to the last quantifiable concentration
BCANS Bureau of Cardiology, Allergy and Neurological Sciences
C_{max} Maximum observed concentration
CI Confidence interval
CRP Canadian Reference Product
HPA Hypothalamic-pitu itary-adrenal axis
HPFB Health Products and Food Branch
K_{el} Terminal elimination constant
OoS Office of Sciences
PAR Perennia l allergic rhinitis
PD Pharm acodynamic
PK Pharm acokinetic
RAT Respiratory and Allergy Therapies
SAC Scientific Advisory Committee
SANDS Supplemental Abbreviated New Drug Submission
SAR Seasonal allergic rhinitis
SCO Serum cortisol
SME Subsequent Market Entry
SNDS Supplemental New Drug Submission
$t_{½}$ Half life

t_{max} Time at maximum concentration
T/R Test -to-reference ratio
TNSS Total Nasal Symptom Score
TPD Therapeutic Products Directorate

5. REFERENCES

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